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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,991	09/16/2003	Leonard F. Bjeldanes	B03-074-1	4613

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
03/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/664,991	BJELDANES ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Appeal Brief filed on 12 October 2008 has been acknowledged and duly made of record.

In view of the above, the Nachschon-Kedmi June 2003 publication is hereby withdrawn because of the Declaration filed by applicant filed on 11 February 2008. In the said Declaration applicants' sufficiently indicate due diligence in preparing, reviewing, revising, and filing this current patent application.

Further, in claim 1 the limitation drawn to *detecting a resultant antiandrogenic response in the host* suggests that the claim may be interpreted broadly. The specification discloses no specific definition drawn to detecting. If interpreted broadly, the claim as disclosed could reasonably mean that the host being administered the antiandrogen would simple *observe* this response upon administration by perceivable changes that normally occur with the adminstration of any active agent. In the case of an anti-androgen that if interpreted broadly, the one in need would observe and/or notice decidedly remarkable changes androgenic-wise.

The application is reopen in favor of the following actions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 (e) that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-7 and 15-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Farley (USPN 6544564 B1).

Principally, Farley teaches [a]n inventive and proprietary formula to enhance the body's natural immune function against viral and infectious diseases and cancer (Abstract only).

Farley teach an immunity system of a human body, against viral and infectious disease and cancer (col. 1, lines 1 and 2).

Further, Farley teaches [that] [t]hese all natural formulas contain phytochemicals that have been shown to cause cell apoptosis, cytotoxicity and inhibition of replication in all of the following cancer cell lines. TBP-1 human monocytic leukaemia cells CaCo-2 human colon cancer cells Human leukaemia HL-60 cells HLA B40-positive breast cancer cells Estrogen receptor positive MCF-7 (human breast cancer cell lines) Estrogen receptor negative MDA-MB-468 (human breast cancer cell lines) Squamous cell carcinoma (SCC) (oral) Androgen-sensitive LNCaP (human prostate) Androgen-insensitive PC-3 cell lines (human prostate)(col. 1 , lines 43-57).

Accordingly, Farley discloses DIM with a range of milligram concentration (col. 1, line 20) (col. 2, line 30-32 and 35).

Based upon the subject matter of Farley *supra,* the inherency is evident with regard to a treatment for cancer. Accordingly, DIM is disclosed in a range of dosages which is clearly anticipatory with regard to treatment. As also disclosed *supra*, Androgen-insensitive PC-3 cell lines is listed as a cancer. Observation of therapeutical effect would have been inherent for a therapeutical method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Safe USPGPUB 2002/0115708 A1).

Safe essentially teach [that] [t]he DIM series of compounds containing both ring and methylene -C substituents can be used for treating multiple cancers through both Ah receptor-dependent and independent pathways. Many of these compounds bind the Ah receptor; however, it is suspected that they may also inhibit tumor growth by other mechanisms, such as through activation of PPAR.gamma. (Example 3). Results illustrated below summarize the concentration-dependent induction of CYP1A1-dependent ethoxyresorufin O-deethylase (EROD) activity by DIM and TCDD in androgen-nonresponsive PC3 human prostate cancer cells (FIG. 12). Initial studies showed that minimal (but significant) induction was observed after 24 hours; however, 10 .mu.M DIM and 10 nM TCDD induced EROD activity which was maximal (for TCDD) after treatment for 96 hours. The fold-induction response for DIM was lower than observed for TCDD even at concentrations of DIM that were 1000 times higher than TCDD, and this response is typical for SahRMs such as DIM which exhibit low Ah receptor-mediated toxicities (Chen et al., "Indole-3-carbinol and diindolylmethane as aryl hydrocarbon (Ah) receptor agonists and antagonists in T47D human breast cancer cells" Biochem. Pharmacol 51:1069-1076, 1996). ***We also investigated the induction of EROD activity in two additional androgen-responsive prostate cancer cell lines. The results illustrated in FIG. 13 show that 0.1 to 10 nM TCDD induced ERODactivity in androgen-responsive 22 Rv1 prostate cancer cells (top), and DIM also induced a minimal (but significant) increase in ERODactivity (middle). In combination studies, higher concentration of DIM inhibited TCDD induced activity, and this is consistent with results of previous studies which show that DIM interacts directly with CYP1A1 protein and inhibits catalytic activity such as EROD***(Chen et al., "Indole-3-carbinol and diindolylmethane as aryl hydrocarbon (Ah) receptor agonists and antagonists in T47D human

breast cancer cells" Biochem. Pharmacol. 51:1069-1076, 1996). We have also investigated the induction of EROD activity by TCDD in androgen-responsive LnCAP prostate cancer cells and there was also significant induction of EROD activity. Thus, human prostate cancer cells express a functional Ah receptor[0071].

Further, Safe teaches methods and compositions for the treatment of a wide array of cancers and tumors. In illustrative embodiments, diindolylmethanes, C-substituted diindolylmethanes, and analogs thereof have been described, which when administered either alone, or in combination with other anti-cancer or anti-tumorigenic compounds, provide new therapies for the treatment of prostate cancer (Abstract, [0050], last line of instant paragraph).

Safe teaches a practicing administration (in vitro and in vivo) to human patients in need thereof via inhibition of prostate cancer cell growth which includes androgen-sensitive and androgen-responsive (including androgen-sensitive, or androgen-responsive) [0065, 0049, 0071].

Safe discloses the directed use of DIM and derivatives thereof for the specific contacting, detecting, and inhibiting via a gel mobility shift assay for prostate cancer cells (Brief description of Drawings – Table CWU – DRTL (1)) in a comparative study to estrogen-dependent pathologies. Safe further discloses the practicing methods of administering said antiandrogenic agent in claims 16, 34, 51, and 69, therein.

Safe teaches derivatives of the practicing DIM core structure that are also taught in the instant application. In said referenced publication on page 3, section [0039] under the heading: Definitions, said structure is disclosed. Derivatives of the core structure are disclosed in the

instant application on page 3 of the specification under the heading: Summary of Invention. Safe discloses in published claims, the *in vitro* method (by use of assays which are disclosed empirical series of method steps used to detect a reaction) of treating cancer, the method comprising obtaining a mammal comprising cancer cells, and administering to the mammal a composition comprising an effective dose of a compound of the said formula. Claims 17-19 are made obvious over claims 16, 34, 51, and 69 in Safe obvious over using this related core structure in the use of treatment against the specific cancer-types, i.e., prostate cancer and pathologies thereof.

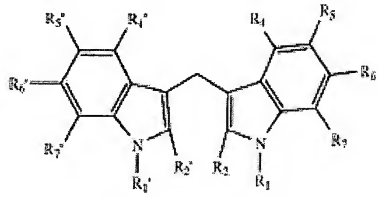
Safe teaches detection on page 5, Example 2, section [0058] in that a process is disclosed where inhibition was determined, i.e., where clear proliferation of cancer cell lines were significantly inhibited. Further, detection is implied in said reference where sensitive cells were noticeably inhibited at the lowest concentration.

Safe, in accordance, more specifically teaches detection on page 4, section [0047] of said referenced publication where resolution of the mixture using chiral chromatography column would result in the isolation of purified or pure enantiomers products. Furthermore, Safe teaches the use of thin-layer chromatography and liquid chromatography in section [0067] (page 6), both well-established detection methods and/or detection facilitators.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made consider the teachings of Safe et al. in obviousness over the claimed invention.

Essentially, Safe et al. teach the scope and content which encompasses the scope and content of the claimed invention. Principally, the scope is drawn to a method of providing an antiandrogen to a host determined to be in need thereof. Safe et al. teach the claimed compound

and/or derivative thereof to be used in the administration of androgenic disorders. Safe et al. teach an in vitro method of treating cancer cells with a compound of formula:



(Please see claim 1 and 36 of Safe et al., page 9 and 11, respectively, (para 90)).

Accordingly, the second step of the current invention does not carry much patentable weight because detecting a resultant antiandrogenic response in the host would reasonably occur due to such a method of administration. Contacting the host with an effective amount of DIM which is an active agent (drug) is art-known to change the molecular physiology of the body. Thus, the limitation directed to detecting is made obvious by any form of administration involving an active agent such as DIM.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

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/SREENI PADMANABHAN/

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